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10/522,333	05/24/2005	Edith Dellacherie	122536	8802
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OLIFF & BERRIDGE, PLC			PALENIK, JEFFREY T	
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ALEXANDRIA, VA 22320-4850			ART UNIT	PAPER NUMBER
			1615	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

OfficeAction25944@oliff.com
jarmstrong@oliff.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,333	DELLACHERIE ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 November 2010.
 2a) This action is **FINAL**. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-19,21-24 and 28-33 is/are pending in the application.
 4a) Of the above claim(s) 8 and 21-24 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-7,9-19 and 28-33 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

STATUS OF THE APPLICATION

Receipt is acknowledged of Applicants' Request for Continued Examination (RCE), filed 12 November 2010, Amendments and Remarks, filed 12 October 2010, in the matter of Application N° 10/522,333. The Examiner further acknowledges the following:

Claims 1-19, 24 and 28-33 are pending, where claims 8 and 21-24 remain withdrawn from consideration.

No claims have been added.

Claim 20 has been cancelled.

Claims 1 and 32 have been amended. Both claims remove the "at least in part" limitation from the recitation. Claim 1 further recites an intended use for the amphiphilic hyaluronan as an emulsion stabilizing agent during the production of the particle by emulsion/solvent evaporation techniques. Support is found in cancelled claim 20.

No new matter has been added.

Thus, claims 1-7, 9-19 and 28-33 continue to represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted for consideration.

MAINTAINED REJECTIONS

The following rejections are maintained from the previous Office Correspondence dated 11 June 2010 since the art which was previously cited continues to read on the amended/newly cited limitations.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 9-13, 16-19, 28, 29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (USPN 4,904,479) [emphasis added to reflect cancelled claim].

The independent claims are directed to a particle having a core and a coating, wherein the core comprises at least one biodegradable organosoluble polymer. The coating is comprised of at least one hyaluronan or one of its derivatives. The hyaluronan-based coating is further characterized as either partially or fully encapsulating the particle as well as being chemically modified via ester or amide functional groups so as to form hydrophobic groups which interact with the polymer core (claims 1, 2, 20 and 32). Claim 3 recites that the group which is esterified to hyaluronan is a linear or branched, saturated or unsaturated alkyl chain. Claim 29 further limits the alkyl group of claim 3 such that it is interrupted with one or more hetero atom(s). “Hetero atoms” are defined by Applicants as including sulfur, oxygen and/or nitrogen atoms (see pg. 4, lines 27-29). Claims 9-11 and 28 recite limitations to the biodegradable organosoluble polymer, such as polylactic acid, polyglycolic acid and copolymers thereof and that it is a natural biodegradable polymer (claim 28).

The invention of Illum is directed to a drug delivery system comprising an active drug as a suspension of colloidal particles, wherein each particle is coated with a material which provides a hydrophilic coat (claim 1). Though the examples and teachings of Illum are primarily directed to a model where the core particles comprise polystyrene and the coating material comprises poloxamer, it is expressly taught and suggested that other materials may be used to

Art Unit: 1615

accomplish practiced invention. Of particular note, Illum teaches that the core particles may include polylactides, polyglycolides and mixtures thereof (e.g. copolymers), whereas coating materials which would provide the same effect as the poloxamers include those which may be esterified to produce suitable hydrophilic and hydrophobic domains. It is further suggested that polymers which may undergo such a modification include hyaluronic acid (col. 10, lines 25-41).

The hydrophobic domains, which are taught as preferably including polyoxypropylene in addition to other hydrophobic groups can be modified into polymer chains, for example by way of esterification of maleic acid groups (col. 2, lines 31-34). Though maleic acid is an uninterrupted aliphatic dicarboxylic acid compound (e.g. linear alkyl), the continued esterification of multiple maleic acid groups, as suggested by Illum, would result in an aliphatic maleic acid polymer interrupted by oxygen atoms.

Claims 12 and 13 recite that the particle core further comprises at least one biological active, such as proteins. Claim 16 recites that the particle core further comprises up to 95% by weight of an active substance.

Illum expressly teaches and suggests that the particle core may be alternatively comprised of monomers and copolymers of PLA and/or PGA. It is further taught and suggested that the polymer mixture may also include the protein albumin (col. 10, lines 25-32). Though there is no percentage of albumin which is expressly taught within the core, it is the position of the Examiner that since the protein can be present in the particle core is suggestion enough that it would be present in an amount greater than 0%, which expressly reads on the instant limitation of up to 95% by weight.

Claims 17 and 31 each further limit the composition of claim 1 with regards to its particle size. Claim 17 recites a particle size range of 50 nm (0.05 microns) to 600 microns, whereas claim 31 recites a range of 80 nm to 230 microns. Claim 18 recites that the particle is a nanoparticle, whereas claim 19 recites the particle as a microparticle. Per Applicants' disclosure, a nanoparticle ranges in size from 1-1,000 nm, whereas a microparticle ranges from 1,000 nm to several thousand microns (see pg. 9, lines 8-11).

Illum teaches expressly teaches the instantly claimed nanoparticle sizes (e.g. 50-60 nm) in the Examples (see for example, Example 1, col. 5, lines 20-21). Again though the practiced invention is directed preferably to polystyrene core particles, as discussed above, the polymer core may be substituted with the aforementioned biodegradable polymers. Regarding Applicants' instant claims directed to the larger microparticle ranges, Illum also discusses conducting performing mouse peritoneal macrophage studies where larger microspheres having a 5.25 micron diameter are used (see e.g. col. 3, lines 40-47).

Thus, in view of the express teachings provided by Illum, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time of the invention to have arrived at a particle composition as instantly claimed. Though the practiced invention of Illum is directed primarily to polystyrene core particles encapsulated with a polyoxyethylene-polyoxypropylene based coating, the ordinarily skilled artisan would have been highly motivated to derive a composition, for example, of a PLA-PGA copolymer core having an esterified hyaluronic acid coating.

Based on the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, alone or in combination, especially in the absence of evidence to the contrary.

Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Illum et al. with respect to claims 1-3, as set forth above, and della Valle et al. (USPN 4,851,521) in further view of McMurry (3rd Ed.; 1992).

The limitations of claims 1-3 are discussed above. Claim 4 recites that the hyaluronic acid of claims 1-3 has esterified to it an alkyl chain comprising five or more carbon atoms. Claim 5 further narrows the chain length to 15-20 carbon atoms and further recites that the alkyl group has a degree of esterification of at most 15%. Claim 6 further narrows claim 5 to a length of 18 carbon atoms. Claim 7 further limits the composition of claim 6 to a degree of esterification of less than 7%.

The teachings of Illum are discussed above. Of particular note is that the practiced invention teaches and suggests the use of esterified hyaluronic acid as a coating composition over core particles composed of homo- or copolymers of PLA and/or PGA. However, Illum does not expressly elaborate on the alkyl groups which are esterified to HA except to suggest that maleic acid groups may be used in the esterification reaction. This deficiency further includes the instantly claimed alkyl chain length and the degree of esterification properties.

The invention of della Valle et al. is directed to the preparation and use of the esters of hyaluronic acid in which all or a portion of which of the carboxylic groups of the acid are esterified (Abstract). The esterified alcohol-based hyaluronic acids are taught as being

applicable in the pharmaceutical field as carriers of pharmaceutical active agents and or carrying vehicles (col. 5, lines 1-5). Alcohols of the aliphatic series to be used as esterifying components of the carboxylic groups of HA according to the invention include those with a maximum of 34 carbon atoms, which may be either saturated or unsaturated as well as optionally substituted with various sulfur-based (e.g. mercaptan), nitrogen-based (e.g. amine) or oxygen-based (e.g. hydroxyide) components (col. 5, lines 27-34). The aforementioned alcohols are further taught as optionally being interrupted in the carbon atom chain by heteroatoms such as oxygen, nitrogen and sulfur atoms (col. 5, lines 48-50). Though della Valle does generally discuss the degree of esterification of HA with regards to the aforementioned alcohol components (col. 8, lines 18-26), specific degrees of esterification are not, such as those which are instantly claimed.

However, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have prepared esterified forms of hyaluronic acid as taught by della Valle and applied them as coating compounds to the PLA and/or PGA copolymer core particles of Illum. The ordinarily skilled artisan would have been highly motivated to do this particularly in view of the aforementioned teaching of Illum where PLA/PGA cores are coated with esterified forms of HA. Regarding Applicants limitations of creating hydrophobic groups in order to hydrophobically “anchor” the coating to the particle (i.e., control the degree of esterification), della Valle further teaches that the degree of esterification of the carboxylic groups of HA using an alcohol (e.g. stearic alcohol) is dependent on the desired end-use properties, such as control of hydrophilicity and hydrophobicity. It is further taught that increasing or decreasing the degree of esterification of HA will control its solubility in water (col. 8, lines 18-26). Thus, in view of the combined teachings, it is the position of the Examiner

that it would have also been well within the purview of the skilled artisan to employ an esterification reaction (e.g. Fischer esterification reaction) in order to arrive at the desired degree of esterification and thus arrive desired number of hydrophobic groups required to anchor the coating to the particle core (see e.g. pp.803-804 of McMurry; 1992). It follows that the reacting HA in this fashion is a result-effective means for optimizing hyaluronic acid that would have been obvious for a person of ordinary skill in the art to employ. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

Based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Illum et al. with respect to claims 1, 12 and 13 as set forth above, and Lee et al (USPN 5,753,234).

The limitations to claims 1, 12 and 13 are discussed above. Claim 14 further limits the composition of claim 13 such that the encapsulated active substance is chosen from glucosamine, hyaluronic acid, chondroitin sulfate and mixtures thereof. Claim 15 further limits the "synthetic active substance" limitation of claim 12 reciting that it comprises a synthetic medicinal product such as anti-inflammatory compounds or antibiotics.

The teachings of Illum are discussed above. Again, of particular note are the teachings whereby the particles prepared by Illum comprise a biodegradable core (e.g. PLA and/or PGA homo- and/or copolymers) and wherein the coating applied may be an esterified form of hyaluronic acid (col. 10, lines 25-41). It should also be noted that the size of particles used taught by the Illum reference range from as small as 50 nm to as large as 5.25 microns. The invention of Illum is deficient in so much as there is no express teaching that the active substance within the PLA/PGA core particle is any of those which are instantly claimed. However, the teachings of Lee et al. rectify this deficiency.

Lee et al. is directed to the preparation of microparticles which range in size from 0.5-300 microns and which are prepared by dissolving one or more antigens in an aqueous solution and removing the residual water to form a core particle. Said active core particles are then coated with a biodegradable polymer (Abstract). Exemplary water-soluble substances are taught as including hyaluronic acid (col. 6, lines 2-5). Exemplary antigens are expressly taught as including antibiotics, antiviral agents and immunizing substances (col. 5, lines 46-55). Exemplary hydrophobic used to encapsulate the cores include PLGA, PGA and PLA, where PLGA and PLA are preferred (col. 6, lines 30-36). The biodegradable polymer is further taught as being used in an amount which ranges as high as 100-times the individual particle weight (col. 6, lines 23-25). It is thus the position of the Examiner that the particles which are prepared by Lee expressly teach the instantly claimed biodegradable polyester core which further encapsulates one or more of the active ingredients of recited in claims 14-15.

Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to have coated the medicated PLA/PGA microparticle prepared by

Lee using a hyaluronic acid-based coating composition as taught by Illum in order to produce the instantly claimed composition. The ordinarily skilled artisan, recognizing that the Illum teachings are directed to using an HA-based coating to encapsulate a biodegradable polyester-based core particle, would also recognize that the Lee invention prepares the same type and size of particles which are coated by Illum. The only exception is that the particles prepared by Lee further encapsulate an active substance. Given that both of the references are directed to the formation of pharmaceutical delivery formulations, the ordinarily skilled artisan would be motivated to modify the teachings of Illum with the particle of Lee in order to control the release of the active ingredient.

Thus, based on the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, alone or in combination, especially in the absence of evidence to the contrary.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the Illum reference (i.e., primary reference) as it pertains to each of the above rejections under 35 USC 103(a) have been fully considered but they are not persuasive. It is understood that Applicants traverse the initial "Illum" rejection in an effort to overcome each of the rejections as they all depend on Illum.

It is noted that Applicants' have provided no additional Remarks to those presented in the After Final response of 12 October 2010.

Applicants' response discusses adding the limitation "wherein said amphiphilic hyaluronan is used as emulsion stabilizing agent during the production of the particle by emulsion/solvent techniques so that the hydrophobic groups are anchored and extend in the polymeric core of the particle."

Applicants reiterate this amendment further arguing that the anchoring of the hydrophobic groups of the hyaluronan occurs during the production of the particle. The Rule 132 Declaration, filed 22 February 2010 and referred to in the Remarks, has been reconsidered by the Examiner, but remains unpersuasive. The crux of the Declaration is directed to the difference in the methods used to prepare the Illum particles versus the instantly claimed particles. It is stated in ¶3 of the Declaration that "[s]trong interactions thus exist between the hyaluronan and the particle core due to hydrophobic interactions inside the matrix between entangled chains of particle-constituting hydrophobic polymer and of hydrophobic groups [bourn] by amphiphilic hyaluronan."

As an initial matter, Applicants' amended limitation "wherein said amphiphilic hyaluronan is used as...", is considered by the Examiner as a recitation of intended use, as discussed in the Advisory Action, mailed 28 October 2010. Amending a "use" for a recited compound in the instant claim does not overcome a showing in the art where a composition comprises said compound. Also, in response to Applicants' Remarks and declared statements directed to the methods for producing the instantly claimed particles, the Examiner respectfully reiterates that said instant invention is directed to a composition rather than its method of production. Per MPEP §2113, "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The

patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

In the instant case, the coated particles produced by Illum are considered to be compositionally similar to those which are instantly claimed. To support this argument, the Examiner respectfully points to Illum where it is clearly disclosed that the “mechanism of action of the materials resides in the structure of the coating agent, namely that it has hydrophobic and hydrophilic [e.g., amphiphilic] domains. The hydrophobic domain will **anchor the coating to the particle surface** and prevent its displacement by plasma proteins.” (Illum; col. 2, lines 25-29). Said coating agents, as discussed in the rejection above, are taught as including polymers modified to have both hydrophobic and hydrophilic domains (e.g., hyaluronic acid) [emphasis added]. As such, it is the position of the Examiner that it would be reasonable to expect that the particle coating of the art will behave the same as that which is instantly claimed, absent a clear showing of evidence to the contrary.

The “anchored and extend in the polymeric core” limitation thus continues to be broadly and reasonably interpreted by the Examiner as being read upon by the interaction of (e.g., intertwining of) the functional groups of the coating composition with those of the surface of the core particle. Such an interaction is considered to anchor portions of the coating composition into the particle core and thus read upon by both adsorption and absorption of a coating to a core [emphasized added].

For these reasons, Applicants' arguments are found unpersuasive. Said rejection is therefore **maintained.**

REQUEST FOR REJOINDER

Applicants' request for rejoinder for non-elected claims 8, 19 and 21-24 based on the allowability of the previously elected product claims has been fully reconsidered, but is not persuasive. Since the presently elected claims are not considered to be in condition for allowance, it follows that the non-elected claims remain presently withdrawn from consideration.

All claims have been rejected; no claims are allowed.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

Art Unit: 1615

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/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner
Art Unit 1615